# Ledipasvir/Sofosbuvir (Harvoni®)

## National Drug Monograph

## November 2014

**VA Pharmacy Benefits Management Services, Medical Advisory Panel,**
**VISN Pharmacist Executives and Office of Public Health**

*The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

## FDA Approval Information[1]

| | |
|---|---|
| **Description/ Mechanism of Action** | Ledipasvir/sofosbuvir is a fixed-dose combination of two direct acting antivirals that have different mechanisms of action. Ledipasvir is a NS5A inhibitor while sofosbuvir is a nucleotide analog NS5B polymerase inhibitor. |
| **Indication(s) under Review in this document** | Ledipasvir/sofosbuvir is indicated for the treatment of chronic hepatitis C genotype 1 infection in adults. |
| **Dosage Form(s) Under Review** | Fixed-dose combination tablet containing 90mg of ledipasvir and 400 mg of sofosbuvir |
| **REMS** | NO REMS |
| **Pregnancy Rating** | Pregnancy Category B |

## Executive Summary[1]

| | |
|---|---|
| Efficacy | • Ledipasvir/sofosbuvir was evaluated in three Phase 3 randomized, open-label studies conducted in HCV genotype 1 patients with compensated liver disease with or without cirrhosis. In two of the trials, patients were randomized to receive ledipasvir/sofosbuvir with or without ribavirin for 12 or 24 weeks. In the other trial, patients were randomized to receive ledipasvir/sofosbuvir with or without ribavirin for 8 weeks or ledipasvir/sofosbuvir for 12 weeks. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment.<br>• Ledipasvir/sofosbuvir with or without ribavirin achieved SVRs in the range of 94-99%. SVRs did not differ in patients receiving ledipasvir/sofosbuvir with or without ribavirin. |
| Safety | • Pooled safety data for ledipasvir/sofosbuvir is available from the three Phase 3 clinical trials. Most common adverse reactions (≥10%) were fatigue and headache. |
| Potential Impact | • Ledipasvir/sofosbuvir is an FDA approved interferon-free regimen for patients with chronic HCV Genotype 1. It is available as a fixed-dose combination of ledipasvir/sofosbuvir that is administered once-daily for either 8, 12, or 24 weeks depending on patient characteristics. |

## Background

**Purpose for review**

The purpose of the review is to evaluate the efficacy and safety of the fixed-dose combination of ledipasvir/sofosbuvir.

**Other therapeutic options**

| Formulary Alternatives for interferon free regimens for HCV Genotype 1 Patients | Other Considerations |
|---|---|
| Sofosbuvir plus simeprevir | 2 pills once a day (i.e., not a fixed-dose combination product)<br><br>Simeprevir plus sofosbuvir should not be used in patients that experienced previous virologic failure with a NS3-4A protease inhibitor containing regimen (e.g., boceprevir or telaprevir). |

## Efficacy (FDA Approved Indications)[1-4]

**Literature Search Summary**
A literature search was performed on PubMed/Medline (1966 to October 2014) using the search terms ledipasvir and Harvoni. The search was limited to studies performed in humans and published in the English language. The pivotal phase 3 clinical trials published in peer-reviewed journals were included.

**Review of Efficacy**
The FDA approval of ledipasvir/sofosbuvir was based on three pivotal Phase 3 randomized, open-label trials (ION-1, ION-2, and ION-3).[1] The ION trials evaluated HCV genotype 1 patients with compensated liver disease with and without cirrhosis for treatment durations of 8, 12 or 24 weeks. Primary efficacy endpoint was sustained viral response (SVR) at 12 weeks post-treatment Secondary endpoint was relapse (i.e., HCV RNA ≥ to lower limit of quantification (LLOQ) with 2 consecutive values or last available post-treatment measurement during the post-treatment period after achieving HCV RNA <LLOQ at end of treatment). Refer to Table 1 for SVRs according to data provided in the prescribing information.[1] Since SVRs did not differ in patients receiving ledipasvir/sofosbuvir with or without ribavirin, the FDA did not report regimens that included ribavirin in the prescribing information. Thus, please note that results from all randomization arms were not included in prescribing information. Refer to Table 2 for SVRs in all randomization arms published in the literature for ION-1, ION-2, and ION-3.[2-4]

**Table 1. Summary of Phase 3 Clinical Trials supporting FDA indications[a]**

| Study | Population | Regimen | SVR12 |
|---|---|---|---|
| ION-1 | Treatment-naïve HCV Genotype 1 patients with or without cirrhosis | LDV/SOF for 12 wks | 210/213 (99%) |
| ION-2 | Treatment-experienced HCV Genotype 1 patients with or without cirrhosis who did not experience SVR after peginterferon/ribavirin with or without a HCV protease inhibitor | LDV/SOF for 12 wks<br>LDV/SOF for 24 wks | 102/109 (94%)<br>108/109 (99%) |
| ION-3 | Treatment-naïve HCV Genotype 1 patients without cirrhosis | LDV/SOF for 8 wks<br>LDV/SOF for 12 wks | 202/215 (94%)<br>208/216 (96%) |

[a]Data reported according to prescribing information[1]; p-values nor 95% CI were not reported; LDV/SOF: ledipasvir/sofosbuvir

**Table 2. Summary of Phase 3 Clinical Trials reported in published literature[2-4]**

| Study | Population | Regimens | SVR12 | 95% CI |
|---|---|---|---|---|
| ION-1 | Treatment-naïve HCV Genotype 1 patients with or without cirrhosis | LDV/SOF for 12 wks<br>LDV/SOF plus ribavirin for 12 wks<br>LDV/SOF for 24 wks<br>LDV/SOF plus ribavirin for 24 wks | 211/214 (99%)<br>211/217 (97%)<br>212/217 (98%)<br>215/217 (99%) | (96 to 100)<br>(94 to 99)<br>(95 to 99)<br>(97 to 100) |
| ION-2 | Treatment-experienced HCV Genotype 1 patients with or without cirrhosis who did not experience SVR after peginterferon/ribavirin with or without HCV protease inhibitor | LDV/SOF for 12 wks<br>LDV/SOF plus ribavirin for 12 wks<br>LDV/SOF for 24 wks<br>LDV/SOF plus ribavirin for 24 wks | 102/109 (94%)<br>107/111 (96%)<br>108/109 (99%)<br>110/111 (99%) | (87 to 97)<br>(91 to 99)<br>(95 to 100)<br>(95 to 100) |
| ION-3 | Treatment-naïve HCV Genotype 1 patients without cirrhosis | LDV/SOF for 8 wks<br>LDV/SOF plus ribavirin for 8 wks<br>LDV/SOF for 12 wks | 202/215 (94%)<br>201/216 (93%)<br>206/216 (95%) | (90 to 97)<br>(89 to 96)<br>(92 to 98) |

Overall Quality of Evidence: High (Refer to Appendix A; note all three pivotal clinical trials sponsored by Gilead); LDV/SOF: ledipasvir/sofosbuvir

**ION-1: Treatment-naïve HCV Genotype 1 patients with or without cirrhosis[1]**

- Randomization in 1:1:1:1 ratio to receive ledipasvir/sofosbuvir for 12 weeks, ledipasvir/sofosbuvir plus ribavirin for 12 weeks, ledipasvir/sofosbuvir for 24 weeks, or ledipasvir/sofosbuvir plus ribavirin for 24 weeks.

- Demographics included median age 54 years old (range: 18 to 80); 59% male; 85% white, 12% black, 12% Hispanic; 79% baseline HCV RNA ≥ 800,000 IU/mL; 67% Genotype 1a; 70% non-C/C IL28B alleles (CT or TT); and 16% cirrhotics.

| | **SVR12** |
|---|---|
| | ledipasvir/sofosbuvir for 12 weeks |
| Overall | 210/213 (99%) |
| Genotype | |
| Genotype 1a | 142/145 (98%) |
| Genotype 1b | 67/67 (100%) |
| Cirrhosis | |
| Without | 176/177 (99%) |
| With | 32/34 (94%) |

P-values not provided in prescribing information

**ION-2: Treatment-experienced HCV Genotype 1 patients with or without cirrhosis who did not experience SVR after peginterferon/ribavirin with or without a HCV protease inhibitor[1]**

- Randomization in 1:1:1:1 ratio to receive ledipasvir/sofosbuvir for 12 weeks, ledipasvir/sofosbuvir plus ribavirin for 12 weeks, ledipasvir/sofosbuvir for 24 weeks, or ledipasvir/sofosbuvir plus ribavirin for 24 weeks.
- Stratification by cirrhosis (with or without), HCV genotype (1a vs 1b), and response to prior HCV therapy (relapse/breakthrough vs nonresponse)
- Demographics included median age 57 years old (range: 24 to 75); 65% male; 81% white, 18% black, 9% Hispanic; 89% baseline HCV RNA ≥ 800,000 IU/mL; 79% Genotype 1a; 88% non-C/C IL28B alleles (CT or TT); and 20% cirrhotics. Of the subjects that failed prior therapy, 47% failed peginterferon /ribavirin while 53% failed protease inhibitor containing regimens.

| | **SVR at 12 weeks** | |
|---|---|---|
| **Subgroups** | **ledipasvir/sofosbuvir 12 week regimen** | **ledipasvir/sofosbuvir 24 week regimen** |
| Overall | 102/109 (94%) | 108/109 (99%) |
| Genotype | | |
| Genotype 1a | 82/86 (95%) | 84/85 (99%) |
| Genotype 1b | 20/23 (87%) | 24/24 (100%) |
| Cirrhosis | | |
| Without | 83/87 (95%) | 85/86 (99%) |
| With | 19/22 (86%) | 22/22 (100%) |
| Prior HCV therapy | | |
| PEG/riba | 40/43 (93%) | 58/58 (100%) |
| PI with PEG/rib | 62/66 (94%) | 49/50 (98%) |
| Response to prior therapy | | |
| Relapse/breakthrough | 57/60 (95%) | 60/60 (100%) |
| Nonresponder | 45/49 (92%) | 48/49 (98%) |

P-values not provided in prescribing information

**ION-3 Treatment-naïve HCV Genotype 1 patients without cirrhosis[1]**

- Randomization in 1:1:1 ratio to receive ledipasvir/sofosbuvir for 8 weeks, ledipasvir/sofosbuvir plus ribavirin for 8 weeks, or ledipasvir/sofosbuvir for 12 weeks.
- Stratification by HCV genotype (1a vs 1b)
- Demographics included median age 55 years old (range: 20 to 75); 58% male; 78% white, 19% black, 6% Hispanic; 81% baseline HCV RNA ≥ 800,000 IU/mL; 80% Genotype 1a; and 73% non-C/C IL28B alleles (CT or TT)
- The pharmaceutical company conducted additional analyses to determine the impact on baseline HCV RNA on SVR; based upon these data, the FDA approved indication states that 8 weeks of ledipasvir/sofosbuvir may be considered in treatment-naïve patients without cirrhosis with baseline HCV RNA <6 million IU/mL.

| | SVR at 12 weeks | |
|---|---|---|
| **Subgroups** | **ledipasvir/sofosbuvir 8 week regimen** | **ledipasvir/sofosbuvir 12 week regimen** |
| Overall[a] | 202/215 (94%) | 208/216 (96%) |
| Genotype | | |
| Genotype 1a | 159/171 (93%) | 165/172 (96%) |
| Genotype 1b | 42/43 (98%) | 43/44 (98%) |
| Baseline HCV RNA | | |
| HCV RNA <6 million IU/mL | 119/123 (97%) | 126/131 (96%) |
| | **Relapse Rates** | |
| Baseline HCV RNA | | |
| HCV RNA <6 million IU/mL | 2/123 (2%) | 2/131 (2%) |
| HCV RNA ≥6 million IU/mL | 9/92 (10%) | 1/85 (1%) |

[a]Difference in SVR between subjects receiving 8 weeks of ledipasvir/sofosbuvir and 12 weeks of ledipasvir/sofosbuvir was –2.3% (97.5% CI –7.2% to 2.5%).

**Summary of efficacy**

- Ledipasvir/sofosbuvir with or without ribavirin achieved SVRs in the range of 94-99%. SVRs did not differ in patients receiving ledipasvir/sofosbuvir with or without ribavirin; therefore, FDA indications are without ribavirin.

## Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM intranet site only).

- Patients with HCV Genotype 3, 4, 5 or 6

## Safety (for more detailed information refer to the product package insert)[1,5]

| | **Comments** |
|---|---|
| **Boxed Warning** | • None |
| **Contraindications** | • None |
| **Warnings/Precautions** | • Use of ledipasvir/sofosbuvir with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.<br>• Use of ledipasvir/sofosbuvir with other products containing sofosbuvir is not recommended. |

**Safety Considerations**

The safety assessment of ledipasvir/sofosbuvir was based on pooled data from three Phase 3 clinical trials of subjects with genotype 1 chronic hepatitis C with compensated liver disease (with and without cirrhosis) including 215, 539, and 326 subjects who received ledipasvir/sofosbuvir for 8, 12 and 24 weeks, respectively.

**Adverse Reactions**

| | |
|---|---|
| Common adverse reactions | Incidence ≥10%: fatigue and headache |
| Death/Serious adverse reactions | No deaths occurred in the Phase 2 and 3 trials that were considered related to study treatment by the investigator. In the pooled phase 3 safety population, 2.6% (51/1952 subjects) of patients overall experienced a serious adverse event (SAE). The incidence of SAEs considered related to study drug by the investigator is <1% (5 subjects) and were the following: headache, salpingitis, mesenteric vein thrombosis and Factor VIII inhibition and anemia. |
| Discontinuations due to adverse reactions | 0%, <1%, and 1% for subjects receiving ledipasvir/sofosbuvir for 8, 12, and 24 weeks, respectively. |
| Laboratory Abnormalities | **Bilirubin elevations:** Bilirubin elevations of greater than 1.5xULN were observed in 3%, <1%, and 2% of subjects treated with ledipasvir/sofosbuvir for 8, 12, and 24 weeks, respectively.<br>**Lipase Elevations:** Transient, asymptomatic lipase elevations of greater than 3xULN were observed in <1%, 2%, and 3% of subjects treated ledipasvir/sofosbuvir with for 8, 12, and 24 weeks, respectively.<br>**Creatine Kinase:** Creatine kinase was not assessed in Phase 3 trials of |

| | |
|---|---|
| | ledipasvir/sofosbuvir. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials. |

**Drug-Drug Interactions**[1]

- Consult the prescribing information prior to use of ledipasvir/sofosbuvir regimen for potential drug interactions.
- Both ledipasvir and sofosbuvir are substrates of drug transporter P-gp and breast cancer resistance protein (BCRP); drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir and ledipasvir plasma concentrations. Ledipasvir is an inhibitor of the drug transporter P-gp and BCRP and may increase intestinal absorption of coadministered substrates for these transporters.
- Ledipasvir/sofosbuvir should NOT be coadministrated with rifampin, rifabutin, rifapentine, St. John's wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, elvitegravir/cobicistat/emtricitabine/tenofovir, tipranavir/ritonavir, simeprevir, or rosuvastatin.
- Other potentially significant drug interactions may include:
    - Ledipasvir/sofosbuvir may increase concentration of digoxin when co-administered; therapeutic monitoring of digoxin is recommended.
    - Ledipsavir/sofosbuvir may increase the concentration of tenofovir when co-administered with certain antiretroviral regimens. Below are recommendations from prescribing information:
        - Efavirenz/Emtricitabine/tenofovir: monitor for tenofovir-associated adverse events
        - Regimens containing tenofovir and a HIV protease inhibitor/ritonavir: Consider alternative HCV or antiretroviral therapy. If co-administration is necessary, monitor for tenofovir-associated adverse events.
- Ledipasvir solubility decreases as pH increases; therefore, drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
    - Separate antacids and ledipasvir/sofosbuvir administration by 4 hours.
    - H2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine 40mg twice daily
    - Proton-pump inhibitor doses comparable to omeprazole 20mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions.

## Risk Evaluation

| As of October 2014 | Comments |
|---|---|
| Sentinel event advisories | • None |
| Look-alike/sound-alike error potentials | • Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List): |

| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
|---|---|---|---|---|
| Ledipasvir/Sofosbuvir 90mg, 400mg tab | None | None | None | Lopinavir<br>Lopinavir/Ritonavir<br>Levemir<br>Sofosbuvir (single agent) |
| Harvoni | None | None | None | Havrix<br>Sovaldi |

## Other Considerations

- None

## Dosing and Administration[1]

Ledipasvir/sofosbuvir is a fixed-dose combination:
One tablet (90mg of ledipasvir and 400mg of sofosbuvir) taken orally once daily with or without food.

Treatment duration is based upon patient characteristics described in the Table below.

| Population includes HCV monoinfected or HCV/HIV-1 co-infected | Total treatment duration |
|---|---|
| **HCV Genotype 1** | |
| **Treatment-naïve without cirrhosis** | |
| Pre-treatment HCV RNA <6 million IU/mL | 12 weeks* |
| Pre-treatment HCV RNA ≥6 million IU/mL | 12 weeks |
| **Treatment-naïve with cirrhosis** | 12 weeks |
| **Treatment-experienced without cirrhosis** | 12 weeks |
| **Treatment-experienced with cirrhosis** | 24 weeks |

**8 weeks of treatment may be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL.

## Special Populations (Adults)[1]

| | Comments |
|---|---|
| **Elderly** | • Clinical trials of ledipasvir/sofosbuvir included 117 subjects aged 65 and over. No overall differences in safety or effectiveness were observed. |
| **Pregnancy** | • Pregnancy Category B |
| **Lactation** | • It is not known whether ledipasvir/sofosbuvir and its metabolites are present in human breast milk. According to PI, the developmental and health benefits of breastfeeding should be considered along with mother's clinical need and potential adverse effects on child from drugs or underlying maternal condition. |
| **Renal Impairment** | • No dosage adjustment is necessary for patients receiving ledipasvir/sofosbuvir with mild or moderate renal impairment; ledipasvir/sofosbuvir was not studied in patients with severe renal impairment (<30mL/min), end-stage renal disease or on hemodialysis. The major metabolite of sofosbuvir is renally excreted and will accumulate in subjects with eGFR <30 mL/min. |
| **Hepatic Impairment** | • No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment. |
| **Pharmacogenetics/genomics** | • No data identified in prescribing information. |

## Projected Place in Therapy

- The VHA Office of Public Health HCV Registry Reports indicates that there were 174,302 Veterans with HCV viremia in VHA care in 2013. More specifically, there were 89,703 HCV Genotype 1 monoinfected viremic Veterans and 3,465 HCV Genotype 1-HIV coinfected Veterans in VHA care in 2013.[6-8]
- Ledipasvir/sofosbuvir is one of two interferon-free regimens used to treat HCV Genotype 1 patients (simeprevir plus sofosbuvir being the other). Ledipasvir/sofosbuvir is available as a convenient fixed-dosed combination. The dosage regimen is one tablet once daily with or without food for a duration of therapy of 8, 12 or 24 weeks depending on patient characteristics.
- Ledipasvir/sofosbuvir achieved SVRs in the range of 94-99% in the Phase 3 clinical trials conducted in treatment-naïve and treatment-experienced HCV patients with compensated liver disease with or without cirrhosis [Overall Quality of Evidence: High (Refer to Appendix A; note all three pivotal clinical trials sponsored by Gilead]. Most common adverse reactions (≥10%) were fatigue and headache.

- Ledipasvir/sofosbuvir has less drug-interactions compared to other direct-acting antiviral regimens; therefore, may be safely co-administered with many of the antiretrovirals and immunosuppressants. However, certain agents should should NOT be co-administered including rifampin, St. John's wort, carbamazepine, phenytoin, phenobarbital, or rosuvastatin. In addition, antacids, H2-receptor antagonists and proton pump inhibitors can decrease absorption of ledipasvir; therefore, consideration of the dose and/or timing is necessary when co-administered with ledipasvir/sofosbuvir.

## References


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**Appendix A: GRADEing the Evidence**

Designations of Quality

| Quality of evidence designation | Description |
|---|---|
| High | Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects). |
| Moderate | Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence. |
| Low | Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes. |

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.